

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use VIREAD safely and effectively. See full prescribing information for VIREAD.

VIREAD (tenofovir disoproxil fumarate) tablet, coated for oral use
Initial U.S. Approval: 2001

WARNINGS: LACTIC ACIDOSIS/SEVERE HEPATOMEGALY WITH STEATOSIS and POST TREATMENT EXACERBATION OF HEPATITIS

See full prescribing information for complete boxed warning.

- Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogs, including VIREAD. (5.1)
- Severe acute exacerbations of hepatitis have been reported in HBV-infected patients who have discontinued anti-hepatitis B therapy, including VIREAD. Hepatic function should be monitored closely in these patients. If appropriate, resumption of anti-hepatitis B therapy may be warranted. (5.2)

RECENT MAJOR CHANGES

| | |
|--|-----------------|
| Boxed Warning | 8/2008, 11/2008 |
| Indications and Usage (1.2) | 8/2008 |
| Dosage and Administration (2.1) | 8/2008 |
| Warnings and Precautions | |
| Exacerbation of Hepatitis after Discontinuation of Treatment (5.2) | 8/2008 |
| Decreases in Bone Mineral Density (5.6) | 11/2008 |
| Early Virologic Failure (5.9) | 11/2008 |

INDICATIONS AND USAGE

VIREAD is a nucleotide analog HIV-1 reverse transcriptase and HBV polymerase inhibitor.

Viread is indicated in combination with other antiretroviral agents for the treatment of HIV-1 infection in adults. (1)

Viread is indicated for the treatment of chronic hepatitis B in adults. (1)

DOSAGE AND ADMINISTRATION

- Recommended dose for the treatment of HIV or chronic hepatitis B: 300 mg once daily taken orally without regard to food. (2.1)
- Dose recommended in renal impairment:
 - Creatinine clearance 30–49 mL/min: 300 mg every 48 hours. (2.2)
 - Creatinine clearance 10–29 mL/min: 300 mg every 72 to 96 hours. (2.2)
 - Hemodialysis: 300 mg every 7 days or after approximately 12 hours of dialysis. (2.2)

DOSAGE FORMS AND STRENGTHS

Tablets: 300 mg. (3)

CONTRAINDICATIONS

None. (4)

WARNINGS AND PRECAUTIONS

- New onset or worsening renal impairment: Can include acute renal failure and Fanconi syndrome. Assess creatinine clearance (CrCl) before initiating

treatment with VIREAD. Monitor CrCl and serum phosphorus in patients at risk. Avoid administering VIREAD with concurrent or recent use of nephrotoxic drugs, including HEPSERA. (5.3)

- Products with same active ingredient: Do not use with other tenofovir-containing products (e.g., ATRIPLA and TRUVADA). (5.4)
- HIV testing: HIV antibody testing should be offered to all HBV-infected patients before initiating therapy with VIREAD. VIREAD should only be used as part of an appropriate antiretroviral combination regimen in HIV-infected patients with or without HBV coinfection. (5.5)
- Decreases in bone mineral density (BMD): Observed in HIV-infected patients. Consider monitoring BMD in patients with a history of pathologic fracture or who are at risk for osteopenia. (5.6)
- Redistribution/accumulation of body fat: Observed in HIV-infected patients receiving antiretroviral combination therapy. (5.7)
- Immune reconstitution syndrome: Observed in HIV-infected patients. May necessitate further evaluation and treatment. (5.8)
- Triple nucleoside-only regimens: Early virologic failure has been reported in HIV-infected patients. Monitor carefully and consider treatment modification. (5.9)

ADVERSE REACTIONS

In HIV-infected patients: Most common adverse reactions (incidence $\geq 10\%$, Grades 2 – 4) are rash, diarrhea, headache, pain, depression, asthenia, and nausea. (6)

In HBV-infected patients: Most common adverse reaction (all grades) was nausea (9%). (6)

To report SUSPECTED ADVERSE REACTIONS, contact Gilead Sciences, Inc. at 1-800-GILEAD-5 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

To report SUSPECTED ADVERSE REACTIONS, contact at or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

DRUG INTERACTIONS

- Didanosine: Coadministration increases didanosine concentrations. Use with caution and monitor for evidence of didanosine toxicity (e.g., pancreatitis, neuropathy). Consider dose reductions or discontinuations of didanosine if warranted. (7.1)
- Atazanavir: Coadministration decreases atazanavir concentrations and increases tenofovir concentrations. Use atazanavir with VIREAD only with additional ritonavir; monitor for evidence of tenofovir toxicity. (7.2)
- Lopinavir/ritonavir: Coadministration increases tenofovir concentrations. Monitor for evidence of tenofovir toxicity. (7.3)

USE IN SPECIFIC POPULATIONS

- Pregnancy: Pregnancy registry available. Enroll patients by calling 1-800-258-4263.
- Nursing mothers: Women infected with HIV should be instructed not to breast feed. (8.3)
- Safety and efficacy not established in patients less than 18 years of age. (8.4)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling

Revised: 07/2009

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FULL PRESCRIBING INFORMATION

WARNINGS: LACTIC ACIDOSIS/SEVERE HEPATOMEGALY WITH STEATOSIS AND POST TREATMENT EXACERBATION OF HEPATITIS

Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogs, including VIREAD, in combination with other antiretrovirals [See *Warnings and Precautions* (5.1)]. Severe acute exacerbations of hepatitis have been reported in HBV-infected patients who have discontinued anti-hepatitis B therapy, including VIREAD. Hepatic function should be monitored closely with both clinical and laboratory follow-up for at least several months in patients who discontinue anti-hepatitis B therapy, including VIREAD. If appropriate, resumption of anti-hepatitis B therapy may be warranted [See *Warnings and Precautions* (5.2)].

1 INDICATIONS AND USAGE

1.1 HIV-1 Infection

VIREAD[®] is indicated in combination with other antiretroviral agents for the treatment of HIV-1 infection.

The following points should be considered when initiating therapy with VIREAD for the treatment of HIV-1 infection:

- VIREAD should not be used in combination with TRUVADA[®] or ATRIPLA[®] [See *Warnings and Precautions* (5.4)].

1.2 Chronic Hepatitis B

VIREAD is indicated for the treatment of chronic hepatitis B in adults.

The following points should be considered when initiating therapy with VIREAD for the treatment of HBV infection:

- This indication is based on data from one year of treatment in primarily nucleoside-treatment-naïve adult patients with HBeAg-positive and HBeAg-negative chronic hepatitis B with compensated liver disease [See *Clinical Efficacy in Patients with Chronic Hepatitis B* (14.2)].
- The numbers of patients in clinical trials who were nucleoside-experienced or who had lamivudine-associated mutations at baseline were too small to reach conclusions of efficacy [See *Clinical Efficacy in Patients with Chronic Hepatitis B* (14.2)].
- VIREAD has not been evaluated in patients with decompensated liver disease.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dose

For the treatment of HIV-1 or chronic hepatitis B: The dose of VIREAD is 300 mg once daily taken orally, without regard to food. In the treatment of chronic hepatitis B, the optimal duration of treatment is unknown.

2.2 Dose Adjustment for Renal Impairment

Significantly increased drug exposures occurred when VIREAD was administered to patients with moderate to severe renal impairment [See *Clinical Pharmacology* (12.3)]. Therefore, the dosing interval of VIREAD should be adjusted in patients with baseline creatinine clearance <50 mL/min using the recommendations in Table 1. These dosing interval recommendations are based on modeling of single-dose pharmacokinetic data in non-HIV and non-HBV infected subjects with varying degrees of renal impairment, including end-stage renal disease requiring hemodialysis. The safety and effectiveness of these dosing interval adjustment recommendations have not been clinically evaluated in patients with moderate or severe renal impairment, therefore clinical response to treatment and renal function should be closely monitored in these patients [See *Warnings and Precautions* (5.3)].

No dose adjustment is necessary for patients with mild renal impairment (creatinine clearance 50–80 mL/min). Routine monitoring of calculated creatinine clearance and serum phosphorus should be performed in patients with mild renal impairment [See *Warnings and Precautions* (5.3)].

Table 1 Dosage Adjustment for Patients with Altered Creatinine Clearance

| | Creatinine Clearance (mL/min)* | | | Hemodialysis Patients |
|---|-----------------------------------|----------------|----------------------|--|
| | ≥50 | 30–49 | 10–29 | |
| Recommended 300 mg Dosing Interval | Every 24 hours | Every 48 hours | Every 72 to 96 hours | Every 7 days or after a total of approximately 12 hours of dialysis† |

*Calculated using ideal (lean) body weight.

†Generally once weekly assuming three hemodialysis sessions a week of approximately 4 hours duration. VIREAD should be administered following completion of dialysis.

The pharmacokinetics of tenofovir have not been evaluated in non-hemodialysis patients with creatinine clearance <10 mL/min; therefore, no dosing recommendation is available for these patients.

3 DOSAGE FORMS AND STRENGTHS

VIREAD is available as tablets. Each tablet contains 300 mg of tenofovir disoproxil fumarate, which is equivalent to 245 mg of tenofovir disoproxil. The tablets are almond-shaped, light blue, film-coated, and debossed with "GILEAD" and "4331" on one side and with "300" on the other side.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Lactic Acidosis/Severe Hepatomegaly with Steatosis

Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogs, including VIREAD, in combination with other antiretrovirals. A majority of these cases have been in women. Obesity and prolonged nucleoside exposure may be risk factors. Particular caution should be exercised when administering nucleoside analogs to any patient with known risk factors for liver disease; however, cases have also been reported in patients with no known risk factors. Treatment with VIREAD should be suspended in any patient who develops clinical or laboratory findings suggestive of lactic acidosis or pronounced hepatotoxicity (which may include hepatomegaly and steatosis even in the absence of marked transaminase elevations).

5.2 Exacerbation of Hepatitis after Discontinuation of Treatment

Discontinuation of anti-HBV therapy, including VIREAD, may be associated with severe acute exacerbations of hepatitis. Patients infected with HBV who discontinue VIREAD should be closely monitored with both clinical and laboratory follow-up for at least several months after stopping treatment. If appropriate, resumption of anti-hepatitis B therapy may be warranted.

5.3 New Onset or Worsening Renal Impairment

Tenofovir is principally eliminated by the kidney. Renal impairment, including cases of acute renal failure and Fanconi syndrome (renal tubular injury with severe hypophosphatemia), has been reported with the use of VIREAD [See *Adverse Reactions* (6.2)]. It is recommended that creatinine clearance be calculated in all patients prior to initiating therapy and as clinically appropriate during therapy with VIREAD. Routine monitoring of calculated creatinine clearance and serum phosphorus should be performed in patients at risk for renal impairment.

Dosing interval adjustment of VIREAD and close monitoring of renal function are recommended in all patients with creatinine clearance <50 mL/min [See *Dosage and Administration* (2.2)]. No safety or efficacy data are available in patients with renal impairment who received VIREAD using these dosing guidelines, so the potential benefit of VIREAD therapy should be assessed against the potential risk of renal toxicity.

VIREAD should be avoided with concurrent or recent use of a nephrotoxic agent.

5.4 Coadministration with Other Products

VIREAD should not be used in combination with the fixed-dose combination products TRUVADA or ATRIPLA since tenofovir disoproxil fumarate is a component of these products.

VIREAD should not be administered in combination with HEPSERA[®] (adefovir dipivoxil) [See *Drug Interactions* (7.4)].

5.5 Patients Coinfected with HIV-1 and HBV

Due to the risk of development of HIV-1 resistance, VIREAD should only be used in HIV-1 and HBV coinfecting patients as part of an appropriate antiretroviral combination regimen.

HIV-1 antibody testing should be offered to all HBV-infected patients before initiating therapy with VIREAD. It is also recommended that all patients with HIV-1 be tested for the presence of chronic hepatitis B before initiating treatment with VIREAD.

5.6 Decreases in Bone Mineral Density

Bone mineral density (BMD) monitoring should be considered for patients who have a history of pathologic bone fracture or are at risk for osteopenia. Although the effect of supplementation with calcium and vitamin D was not studied, such supplementation may be beneficial for all patients. If bone abnormalities are suspected then appropriate consultation should be obtained.

In HIV-infected patients treated with VIREAD in Study 903 through 144 weeks, decreases from baseline in BMD were seen at the lumbar spine and hip in both arms of the study. At Week 144, there was a significantly greater mean percentage decrease from baseline in BMD at the lumbar spine in patients receiving VIREAD + lamivudine + efavirenz (-2.2% ± 3.9) compared with patients receiving stavudine + lamivudine + efavirenz (-1.0% ± 4.6). Changes in BMD at the hip were similar between the two treatment groups (-2.8% ± 3.5 in the VIREAD group vs. -2.4% ± 4.5 in the stavudine group). In both groups, the majority of the reduction in BMD occurred in the first 24–48 weeks of the study and this reduction was sustained through Week 144. Twenty-eight percent of VIREAD-treated patients vs. 21% of the stavudine-treated patients lost at least 5% of BMD at the spine or 7% of BMD at the hip. Clinically relevant fractures (excluding fingers and toes) were reported in 4 patients in the VIREAD group and 6 patients in the stavudine group. In addition, there were significant increases in biochemical markers of bone metabolism (serum bone-specific alkaline phosphatase, serum osteocalcin, serum C-telopeptide, and urinary N-telopeptide) in the VIREAD group relative to the stavudine group, suggesting increased bone turnover. Serum parathyroid hormone levels and 1,25 Vitamin D levels were also higher in the VIREAD group. Except for bone specific alkaline phosphatase, these changes resulted in values that remained within the normal range. The effects of VIREAD-associated changes in BMD and biochemical markers on long-term bone health and future fracture risk are unknown.

Cases of osteomalacia (associated with proximal renal tubulopathy and which may contribute to fractures) have been reported in association with the use of VIREAD [See *Adverse Reactions* (6.2)].

The bone effects of VIREAD have not been studied in patients with chronic HBV infection.

5.7 Fat Redistribution

In HIV-infected patients redistribution/accumulation of body fat including central obesity, dorsocervical fat enlargement (buffalo hump), peripheral wasting, facial wasting, breast enlargement, and "cushingoid appearance" have been observed in patients receiving combination antiretroviral therapy. The mechanism and long-term consequences of these events are currently unknown. A causal relationship has not been established.

5.8 Immune Reconstitution Syndrome

Immune reconstitution syndrome has been reported in HIV-infected patients treated with combination antiretroviral therapy, including VIREAD. During the initial phase of combination antiretroviral treatment, patients whose immune system responds may develop an inflammatory response to indolent or residual opportunistic infections [such as *Mycobacterium avium* infection, cytomegalovirus, *Pneumocystis jirovecii* pneumonia (PCP), or tuberculosis], which may necessitate further evaluation and treatment.

5.9 Early Virologic Failure

Clinical studies in HIV-infected patients have demonstrated that certain regimens that only contain three nucleoside reverse transcriptase inhibitors (NRTI) are generally less effective than triple drug regimens containing two NRTIs in combination with either a non-nucleoside reverse transcriptase inhibitor or a HIV-1 protease inhibitor. In particular, early virological failure and high rates of resistance substitutions have been reported. Triple nucleoside regimens should therefore be used with caution. Patients on a therapy utilizing a triple nucleoside-only regimen should be carefully monitored and considered for treatment modification.

6 ADVERSE REACTIONS

The following adverse reactions are discussed in other sections of the labeling:

- Lactic Acidosis/Severe Hepatomegaly with Steatosis [See Boxed Warning, Warnings and Precautions (5.1)].
- Severe Acute Exacerbation of Hepatitis [See Boxed Warning, Warnings and Precautions (5.2)].
- New Onset or Worsening Renal Impairment [See Warnings and Precautions (5.3)].
- Decreases in Bone Mineral Density [See Warnings and Precautions (5.6)].
- Immune Reconstitution Syndrome [See Warnings and Precautions (5.8)].

6.1 Adverse Reactions from Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Clinical Trials in Patients with HIV Infection

More than 12,000 patients have been treated with VIREAD alone or in combination with other antiretroviral medicinal products for periods of 28 days to 215 weeks in clinical trials and expanded access studies. A total of 1,544 patients have received VIREAD 300 mg once daily in clinical trials; over 11,000 patients have received VIREAD in expanded access studies.

The most common adverse reactions (incidence $\geq 10\%$, Grades 2–4) identified from any of the 3 large controlled clinical trials include rash, diarrhea, headache, pain, depression, asthenia, and nausea.

Treatment-Naïve Patients

Study 903 - Treatment-Emergent Adverse Reactions: The most common adverse reactions seen in a double-blind comparative controlled study in which 600 treatment-naïve patients received VIREAD (N=299) or stavudine (N=301) in combination with lamivudine and efavirenz for 144 weeks (Study 903) were mild to moderate gastrointestinal events and dizziness.

Mild adverse reactions (Grade 1) were common with a similar incidence in both arms, and included dizziness, diarrhea, and nausea. Selected treatment-emergent moderate to severe adverse reactions are summarized in Table 2.

Table 2 Selected Treatment-Emergent Adverse Reactions* (Grades 2–4) Reported in $\geq 5\%$ in Any Treatment Group in Study 903 (0–144 Weeks)

| | VIREAD + 3TC + EFV | d4T + 3TC + EFV |
|----------------------------|--------------------|-----------------|
| | N=299 | N=301 |
| Body as a Whole | | |
| Headache | 14% | 17% |
| Pain | 13% | 12% |
| Fever | 8% | 7% |
| Abdominal pain | 7% | 12% |
| Back pain | 9% | 8% |
| Asthenia | 6% | 7% |
| Digestive System | | |
| Diarrhea | 11% | 13% |
| Nausea | 8% | 9% |
| Dyspepsia | 4% | 5% |
| Vomiting | 5% | 9% |
| Metabolic Disorders | | |
| Lipodystrophy [†] | 1% | 8% |
| Musculoskeletal | | |
| Arthralgia | 5% | 7% |
| Myalgia | 3% | 5% |
| Nervous System | | |
| Depression | 11% | 10% |
| Insomnia | 5% | 8% |

| | | |
|--|-----|-----|
| Dizziness | 3% | 6% |
| Peripheral neuropathy [‡] | 1% | 5% |
| Anxiety | 6% | 6% |
| Respiratory Pneumonia | 5% | 5% |
| Skin and Appendages Rash event [§] | 18% | 12% |

*Frequencies of adverse reactions are based on all treatment-emergent adverse events, regardless of relationship to study drug.

[†]Lipodystrophy represents a variety of investigator-described adverse events not a protocol-defined syndrome.

[‡]Peripheral neuropathy includes peripheral neuritis and neuropathy.

[§]Rash event includes rash, pruritus, maculopapular rash, urticaria, vesicubullous rash, and pustular rash.

Laboratory Abnormalities: With the exception of fasting cholesterol and fasting triglyceride elevations that were more common in the stavudine group (40% and 9%) compared with VIREAD (19% and 1%) respectively, laboratory abnormalities observed in this study occurred with similar frequency in the VIREAD and stavudine treatment arms. A summary of Grade 3 and 4 laboratory abnormalities is provided in Table 3.

Table 3 Grade 3/4 Laboratory Abnormalities Reported in ≥1% of VIREAD-Treated Patients in Study 903 (0–144 Weeks)

| | VIREAD + 3TC + EFV | d4T + 3TC + EFV |
|--|---------------------------|------------------------|
| | N=299 | N=301 |
| Any ≥ Grade 3 Laboratory Abnormality | 36% | 42% |
| Fasting Cholesterol (>240 mg/dL) | 19% | 40% |
| Creatine Kinase (M: >990 U/L) (F: >845 U/L) | 12% | 12% |
| Serum Amylase (>175 U/L) | 9% | 8% |
| AST (M: >180 U/L) (F: >170 U/L) | 5% | 7% |
| ALT (M: >215 U/L) (F: >170 U/L) | 4% | 5% |
| Hematuria (>100 RBC/HPF) | 7% | 7% |
| Neutrophils (<750/mm ³) | 3% | 1% |
| Fasting Triglycerides (>750 mg/dL) | 1% | 9% |

Study 934 - Treatment Emergent Adverse Reactions: In Study 934, 511 antiretroviral-naïve patients received either VIREAD + EMTRIVA[®] administered in combination with efavirenz (N=257) or zidovudine/lamivudine administered in combination with efavirenz (N=254). Adverse reactions observed in this study were generally consistent with those seen in previous studies in treatment-experienced or treatment-naïve patients (Table 4).

Table 4 Selected Treatment-Emergent Adverse Reactions* (Grades 2–4) Reported in ≥5% in Any Treatment Group in Study 934 (0–144 Weeks)

| | VIREAD[†] + FTC + EFV | AZT/3TC + EFV |
|---|---------------------------------------|----------------------|
| | N=257 | N=254 |
| Gastrointestinal Disorder | | |
| Diarrhea | 9% | 5% |
| Nausea | 9% | 7% |
| Vomiting | 2% | 5% |
| General Disorders and Administration Site Condition | | |

| | | |
|--|----|----|
| Fatigue | 9% | 8% |
| Infections and Infestations | | |
| Sinusitis | 8% | 4% |
| Upper respiratory tract infections | 8% | 5% |
| Nasopharyngitis | 5% | 3% |
| Nervous System Disorders | | |
| Headache | 6% | 5% |
| Dizziness | 8% | 7% |
| Psychiatric Disorders | | |
| Depression | 9% | 7% |
| Insomnia | 5% | 7% |
| Skin and Subcutaneous Tissue Disorders | | |
| Rash event [†] | 7% | 9% |

*Frequencies of adverse reactions are based on all treatment-emergent adverse events, regardless of relationship to study drug.

[†]From Weeks 96 to 144 of the study, patients received TRUVADA with efavirenz in place of VIREAD + EMTRIVA with efavirenz.

[‡]Rash event includes rash, exfoliative rash, rash generalized, rash macular, rash maculo-papular, rash pruritic, and rash vesicular.

Laboratory Abnormalities: Laboratory abnormalities observed in this study were generally consistent with those seen in previous studies (Table 5).

Table 5 Significant Laboratory Abnormalities Reported in ≥1% of Patients in Any Treatment Group in Study 934 (0–144 Weeks)

| | VIREAD* + FTC + EFV | AZT/3TC + EFV |
|---|----------------------------|----------------------|
| | N=257 | N=254 |
| Any ≥ Grade 3 Laboratory Abnormality | 30% | 26% |
| Fasting Cholesterol (>240 mg/dL) | 22% | 24% |
| Creatine Kinase (M: >990 U/L) (F: >845 U/L) | 9% | 7% |
| Serum Amylase (>175 U/L) | 8% | 4% |
| Alkaline Phosphatase (>550 U/L) | 1% | 0% |
| AST (M: >180 U/L) (F: >170 U/L) | 3% | 3% |
| ALT (M: >215 U/L) (F: >170 U/L) | 2% | 3% |
| Hemoglobin (<8.0 mg/dL) | 0% | 4% |
| Hyperglycemia (>250 mg/dL) | 2% | 1% |
| Hematuria (>75 RBC/HPF) | 3% | 2% |
| Glycosuria (≥3+) | <1% | 1% |
| Neutrophils (<750/mm ³) | 3% | 5% |
| Fasting Triglycerides (>750 mg/dL) | 4% | 2% |

*From Weeks 96 to 144 of the study, patients received TRUVADA with efavirenz in place of VIREAD + EMTRIVA with efavirenz.

Treatment-Experienced Patients

Treatment-Emergent Adverse Reactions: The adverse reactions seen in treatment experienced patients were generally consistent with those seen in treatment naïve patients including mild to moderate gastrointestinal events, such as nausea, diarrhea, vomiting, and flatulence. Less than 1% of patients discontinued participation in the clinical studies due to gastrointestinal adverse reactions (Study 907).

A summary of moderate to severe, treatment-emergent adverse reactions that occurred during the first 48 weeks of Study 907 is provided in Table 6.

Table 6 Selected Treatment-Emergent Adverse Reactions* (Grades 2–4) Reported in ≥3% in Any Treatment Group in Study 907 (0–48 Weeks)

| | VIREAD (N=368) (Week 0–24) | Placebo (N=182) (Week 0–24) | VIREAD (N=368) (Week 0–48) | Placebo Crossover to VIREAD (N=170) (Week 24–48) |
|------------------------------------|---|--|---|---|
| Body as a Whole | | | | |
| Asthenia | 7% | 6% | 11% | 1% |
| Pain | 7% | 7% | 12% | 4% |
| Headache | 5% | 5% | 8% | 2% |
| Abdominal pain | 4% | 3% | 7% | 6% |
| Back pain | 3% | 3% | 4% | 2% |
| Chest pain | 3% | 1% | 3% | 2% |
| Fever | 2% | 2% | 4% | 2% |
| Digestive System | | | | |
| Diarrhea | 11% | 10% | 16% | 11% |
| Nausea | 8% | 5% | 11% | 7% |
| Vomiting | 4% | 1% | 7% | 5% |
| Anorexia | 3% | 2% | 4% | 1% |
| Dyspepsia | 3% | 2% | 4% | 2% |
| Flatulence | 3% | 1% | 4% | 1% |
| Respiratory | | | | |
| Pneumonia | 2% | 0% | 3% | 2% |
| Nervous System | | | | |
| Depression | 4% | 3% | 8% | 4% |
| Insomnia | 3% | 2% | 4% | 4% |
| Peripheral neuropathy [†] | 3% | 3% | 5% | 2% |
| Dizziness | 1% | 3% | 3% | 1% |
| Skin and Appendage | | | | |
| Rash event [‡] | 5% | 4% | 7% | 1% |
| Sweating | 3% | 2% | 3% | 1% |
| Musculoskeletal | | | | |
| Myalgia | 3% | 3% | 4% | 1% |
| Metabolic | | | | |
| Weight loss | 2% | 1% | 4% | 2% |

*Frequencies of adverse reactions are based on all treatment-emergent adverse events, regardless of relationship to study drug.

[†]Peripheral neuropathy includes peripheral neuritis and neuropathy.

[‡]Rash event includes rash, pruritus, maculopapular rash, urticaria, vesicubullous rash, and pustular rash.

Laboratory Abnormalities: Laboratory abnormalities observed in this study occurred with similar frequency in the VIREAD and placebo-treated groups. A summary of Grade 3 and 4 laboratory abnormalities is provided in Table 7.

Table 7 Grade 3/4 Laboratory Abnormalities Reported in ≥1% of VIREAD-Treated Patients in Study 907 (0–48 Weeks)

| | VIREAD (N=368) (Week 0–24) | Placebo (N=182) (Week 0–24) | VIREAD (N=368) (Week 0–48) | Placebo Crossover to VIREAD (N=170) (Week 24–48) |
|--------------------------------------|---|--|---|---|
| Any ≥ Grade 3 Laboratory Abnormality | 25% | 38% | 35% | 34% |
| Triglycerides (>750 mg/dL) | 8% | 13% | 11% | 9% |
| Creatine Kinase (M: >990U/L) | 7% | 14% | 12% | 12% |

| | | | | |
|---------------------------------------|----|----|----|----|
| (F: >845 U/L) | | | | |
| Serum Amylase (>175 U/L) | 6% | 7% | 7% | 6% |
| Glycosuria (≥3+) | 3% | 3% | 3% | 2% |
| AST (M: >180 U/L) (F: >170 U/L) | 3% | 3% | 4% | 5% |
| ALT (M: >215 U/L) (F: >170 U/L) | 2% | 2% | 4% | 5% |
| Serum Glucose (>250 U/L) | 2% | 4% | 3% | 3% |
| Neutrophils (<750/mm ³) | 1% | 1% | 2% | 1% |

Clinical Trials in Patients with Chronic Hepatitis B

Treatment-Emergent Adverse Reactions: In controlled clinical trials in patients with chronic hepatitis B, more patients treated with VIREAD experienced nausea: 9% with VIREAD versus 2% with HEPSERA. Other treatment-emergent adverse reactions reported in >5% of patients treated with VIREAD included: abdominal pain, diarrhea, headache, dizziness, fatigue, nasopharyngitis, back pain and skin rash.

Laboratory Abnormalities: A summary of Grade 3 and 4 laboratory abnormalities is provided in Table 8.

Table 8. Grade 3/4 Laboratory Abnormalities Reported in ≥1% of VIREAD-Treated Patients in Studies 0102 and 0103 (0-48 Weeks)

| | VIREAD (N=426) | HEPSERA (N=215) |
|--|---------------------------|----------------------------|
| Any ≥ Grade 3 Laboratory Abnormality | 19% | 13% |
| Creatine Kinase (M: >990U/L) (F: >845 U/L) | 2% | 3% |
| Serum Amylase (>175 U/L) | 4% | 1% |
| Glycosuria (≥3+) | 3% | <1% |
| AST (M: >180 U/L) (F: >170 U/L) | 4% | 4% |
| ALT (M: >215 U/L) (F: >170 U/L) | 10% | 6% |

The overall incidence of on-treatment ALT elevations (defined as serum ALT >2 × baseline and >10 × ULN, with or without associated symptoms) was similar between VIREAD (2.6%) and HEPSERA (2%). ALT elevations generally occurred within the first 4–8 weeks of treatment and were accompanied by decreases in HBV DNA levels. No patient had evidence of decompensation. ALT flares typically resolved within 4 to 8 weeks without changes in study medication.

6.2 Postmarketing Experience

The following adverse reactions have been identified during postapproval use of VIREAD. Because postmarketing reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Immune System Disorders

allergic reaction

Metabolism and Nutrition Disorders

lactic acidosis, hypokalemia, hypophosphatemia

Respiratory, Thoracic, and Mediastinal Disorders

dyspnea

Gastrointestinal Disorders

pancreatitis, increased amylase, abdominal pain

Hepatobiliary Disorders

hepatic steatosis, hepatitis, increased liver enzymes (most commonly AST, ALT gamma GT)

Skin and Subcutaneous Tissue Disorders

rash

Musculoskeletal and Connective Tissue Disorders

rhabdomyolysis, osteomalacia (manifested as bone pain and which may contribute to fractures), muscular weakness, myopathy

Renal and Urinary Disorders

acute renal failure, renal failure, acute tubular necrosis, Fanconi syndrome, proximal renal tubulopathy, interstitial nephritis (including acute cases), nephrogenic diabetes insipidus, renal insufficiency, increased creatinine, proteinuria, polyuria

General Disorders and Administration Site Conditions

asthenia

The following adverse reactions, listed under the body system headings above, may occur as a consequence of proximal renal tubulopathy: rhabdomyolysis, osteomalacia, hypokalemia, muscular weakness, myopathy, hypophosphatemia.

7 DRUG INTERACTIONS

This section describes clinically relevant drug interactions with VIREAD. Drug interactions studies are described elsewhere in the labeling [*See Clinical Pharmacology (12.3)*].

7.1 Didanosine

Coadministration of VIREAD and didanosine should be undertaken with caution and patients receiving this combination should be monitored closely for didanosine-associated adverse reactions. Didanosine should be discontinued in patients who develop didanosine-associated adverse reactions.

When administered with VIREAD, C_{max} and AUC of didanosine (administered as either the buffered or enteric-coated formulation) increased significantly [*See Clinical Pharmacology (12.3)*]. The mechanism of this interaction is unknown. Higher didanosine concentrations could potentiate didanosine-associated adverse reactions, including pancreatitis and neuropathy. Suppression of $CD4^+$ cell counts has been observed in patients receiving tenofovir disoproxil fumarate (tenofovir DF) with didanosine 400 mg daily. In adults weighing >60 kg, the didanosine dose should be reduced to 250 mg when it is coadministered with VIREAD. Data are not available to recommend a dose adjustment of didanosine for patients weighing <60 kg. When coadministered, VIREAD and didanosine EC may be taken under fasted conditions or with a light meal (<400 kcal, 20% fat). Coadministration of didanosine buffered tablet formulation with VIREAD should be under fasted conditions.

7.2 Atazanavir

Atazanavir has been shown to increase tenofovir concentrations [*See Clinical Pharmacology (12.3)*]. The mechanism of this interaction is unknown. Patients receiving atazanavir and VIREAD should be monitored for VIREAD-associated adverse reactions. VIREAD should be discontinued in patients who develop VIREAD-associated adverse reactions.

VIREAD decreases the AUC and C_{min} of atazanavir [*See Clinical Pharmacology (12.3)*]. When coadministered with VIREAD, it is recommended that atazanavir 300 mg is given with ritonavir 100 mg. Atazanavir without ritonavir should not be coadministered with VIREAD.

7.3 Lopinavir/Ritonavir

Lopinavir/ritonavir has been shown to increase tenofovir concentrations [*See Clinical Pharmacology (12.3)*]. The mechanism of this interaction is unknown. Patients receiving lopinavir/ritonavir and VIREAD should be monitored for VIREAD-associated adverse reactions. VIREAD should be discontinued in patients who develop VIREAD-associated adverse reactions.

7.4 Drugs Affecting Renal Function

Since tenofovir is primarily eliminated by the kidneys [*See Clinical Pharmacology (12.3)*], coadministration of VIREAD with drugs that reduce renal function or compete for active tubular secretion may increase serum concentrations of tenofovir and/or increase the concentrations of other renally eliminated drugs. Some examples include, but are not limited to, cidofovir, acyclovir, valganciclovir, ganciclovir, and valganciclovir. Drugs that decrease renal function may also increase serum concentrations of tenofovir.

In the treatment of chronic hepatitis B, VIREAD should not be administered in combination with HEPSERA (adefovir dipivoxil).

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category B

Reproduction studies have been performed in rats and rabbits at doses up to 14 and 19 times the human dose based on body surface area comparisons and revealed no evidence of impaired fertility or harm to the fetus due to tenofovir. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, VIREAD should be used during pregnancy only if clearly needed.

Antiretroviral Pregnancy Registry: To monitor fetal outcomes of pregnant women exposed to VIREAD, an Antiretroviral Pregnancy Registry has been established. Healthcare providers are encouraged to register patients by calling 1-800-258-4263.

8.3 Nursing Mothers

Nursing Mothers: The Centers for Disease Control and Prevention recommend that HIV-1-infected mothers not breast-feed their infants to avoid risking postnatal transmission of HIV-1. Studies in rats have demonstrated that tenofovir is secreted in milk. It is not known whether tenofovir is excreted in human milk. Because of both the potential for HIV-1 transmission and the potential for serious adverse reactions in nursing infants, **mothers should be instructed not to breast-feed if they are receiving VIREAD.**

8.4 Pediatric Use

Safety and effectiveness in patients less than 18 years of age have not been established.

8.5 Geriatric Use

Clinical studies of VIREAD did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. In general, dose selection for the elderly patient should be cautious, keeping in mind the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

8.6 Patients with Impaired Renal Function

It is recommended that the dosing interval for VIREAD be modified in patients with creatinine clearance <50 mL/min or in patients with ESRD who require dialysis [See *Dosage and Administration* (2.2), *Clinical Pharmacology* (12.3)].

10 OVERDOSAGE

Limited clinical experience at doses higher than the therapeutic dose of VIREAD 300 mg is available. In Study 901, 600 mg tenofovir disoproxil fumarate was administered to 8 patients orally for 28 days. No severe adverse reactions were reported. The effects of higher doses are not known.

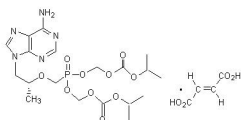
If overdose occurs the patient must be monitored for evidence of toxicity, and standard supportive treatment applied as necessary. Tenofovir is efficiently removed by hemodialysis with an extraction coefficient of approximately 54%. Following a single 300 mg dose of VIREAD, a four-hour hemodialysis session removed approximately 10% of the administered tenofovir dose.

11 DESCRIPTION

VIREAD is the brand name for tenofovir disoproxil fumarate (a prodrug of tenofovir) which is a fumaric acid salt of bis-isopropoxycarbonyloxymethyl ester derivative of tenofovir. In vivo tenofovir disoproxil fumarate is converted to tenofovir, an acyclic nucleoside phosphonate (nucleotide) analog of adenosine 5'-monophosphate. Tenofovir exhibits activity against HIV-1 reverse transcriptase.

The chemical name of tenofovir disoproxil fumarate is 9-[(R)-2-

[[bis[[[(isopropoxycarbonyl)oxy]methoxy]phosphinyl]methoxy]propyl]adenine fumarate (1:1). It has a molecular formula of $C_{19}H_{30}N_5O_{10}P \cdot C_4H_4O_4$ and a molecular weight of 635.52. It has the following structural formula:



Tenofovir disoproxil fumarate is a white to off-white crystalline powder with a solubility of 13.4 mg/mL in distilled water at 25 °C. It has an octanol/phosphate buffer (pH 6.5) partition coefficient (log p) of 1.25 at 25 °C.

VIREAD tablets are for oral administration. Each tablet contains 300 mg of tenofovir disoproxil fumarate, which is equivalent to 245 mg of tenofovir disoproxil, and the following inactive ingredients: croscarmellose sodium, lactose monohydrate, magnesium stearate, microcrystalline cellulose, and pregelatinized starch. The tablets are coated with Opadry II Y-30-10671-A, which contains FD&C blue #2 aluminum lake, hydroxypropyl methylcellulose 2910, lactose monohydrate, titanium dioxide, and triacetin.

In this insert, all dosages are expressed in terms of tenofovir disoproxil fumarate except where otherwise noted.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Tenofovir disoproxil fumarate is an antiviral drug [See *Clinical Pharmacology* (12.4)].

12.3 Pharmacokinetics

The pharmacokinetics of tenofovir disoproxil fumarate have been evaluated in healthy volunteers and HIV-1 infected individuals. Tenofovir pharmacokinetics are similar between these populations.

Absorption

VIREAD is a water soluble diester prodrug of the active ingredient tenofovir. The oral bioavailability of tenofovir from VIREAD in fasted patients is approximately 25%. Following oral administration of a single dose of VIREAD 300 mg to HIV-1 infected patients in the fasted state, maximum serum concentrations (C_{max}) are achieved in 1.0 ± 0.4 hrs. C_{max} and AUC values are 0.30 ± 0.09 µg/mL and 2.29 ± 0.69 µg·hr/mL, respectively.

The pharmacokinetics of tenofovir are dose proportional over a VIREAD dose range of 75 to 600 mg and are not affected by repeated dosing.

Distribution

In vitro binding of tenofovir to human plasma or serum proteins is less than 0.7 and 7.2%, respectively, over the tenofovir concentration range 0.01 to 25 µg/mL. The volume of distribution at steady-state is 1.3 ± 0.6 L/kg and 1.2 ± 0.4 L/kg, following intravenous administration of tenofovir 1.0 mg/kg and 3.0 mg/kg.

Metabolism and Elimination

In vitro studies indicate that neither tenofovir disoproxil nor tenofovir are substrates of CYP enzymes.

Following IV administration of tenofovir, approximately 70–80% of the dose is recovered in the urine as unchanged tenofovir within 72 hours of dosing. Following single dose, oral administration of VIREAD, the terminal elimination half-life of tenofovir is approximately 17 hours. After multiple oral doses of VIREAD 300 mg once daily (under fed conditions), $32 \pm 10\%$ of the administered dose is recovered in urine over 24 hours.

Tenofovir is eliminated by a combination of glomerular filtration and active tubular secretion. There may be competition for elimination with other compounds that are also renally eliminated.

Effects of Food on Oral Absorption

Administration of VIREAD following a high-fat meal (~700 to 1000 kcal containing 40 to 50% fat) increases the oral bioavailability, with an increase in tenofovir $AUC_{0-\infty}$ of approximately 40% and an increase in C_{max} of approximately 14%. However, administration of VIREAD with a light meal did not have a significant effect on the pharmacokinetics of tenofovir when compared to fasted administration of the drug. Food delays the time to tenofovir C_{max} by approximately 1 hour. C_{max} and AUC of tenofovir are 0.33 ± 0.12 µg/mL and 3.32 ± 1.37 µg·hr/mL following multiple doses of VIREAD 300 mg once daily in the fed state, when meal content was not controlled.

Special Populations

Race: There were insufficient numbers from racial and ethnic groups other than Caucasian to adequately determine potential pharmacokinetic differences among these populations.

Gender: Tenofovir pharmacokinetics are similar in male and female patients.

Pediatric and Geriatric Patients: Pharmacokinetic studies have not been performed in children (<18 years) or in the elderly (>65 years).

Patients with Impaired Renal Function: The pharmacokinetics of tenofovir are altered in patients with renal impairment [See *Warnings and Precautions* (5.3)]. In patients with creatinine clearance <50 mL/min or with end-stage renal disease (ESRD) requiring dialysis, C_{max} , and $AUC_{0-\infty}$ of tenofovir were increased (Table 9). It is recommended that the dosing interval for VIREAD be modified in patients with creatinine clearance <50 mL/min or in patients with ESRD who require dialysis [See *Dosage and Administration* (2.2)].

Table 9 Pharmacokinetic Parameters (Mean \pm SD) of Tenofovir* in Patients with Varying Degrees of Renal Function

| Baseline Creatinine Clearance (mL/min) | >80 (N=3) | 50–80 (N=10) | 30–49 (N=8) | 12–29 (N=11) |
|---|---------------------|---------------------|--------------------|---------------------|
| C_{max} (µg/mL) | 0.34 ± 0.03 | 0.33 ± 0.06 | 0.37 ± 0.16 | 0.60 ± 0.19 |
| $AUC_{0-\infty}$ (µg·hr/mL) | 2.18 ± 0.26 | 3.06 ± 0.93 | 6.01 ± 2.50 | 15.98 ± 7.22 |
| CL/F (mL/min) | 1043.7 ± 115.4 | 807.7 ± 279.2 | 444.4 ± 209.8 | 177.0 ± 97.1 |
| CL _{renal} (mL/min) | 243.5 ± 33.3 | 168.6 ± 27.5 | 100.6 ± 27.5 | 43.0 ± 31.2 |

*300 mg, single dose of VIREAD

Tenofovir is efficiently removed by hemodialysis with an extraction coefficient of approximately 54%. Following a single 300 mg dose of VIREAD, a four-hour hemodialysis session removed approximately 10% of the administered tenofovir dose.

Patients with Hepatic Impairment: The pharmacokinetics of tenofovir following a 300 mg single dose of VIREAD have been studied in non-HIV infected patients with moderate to severe hepatic impairment. There were no substantial alterations in tenofovir

pharmacokinetics in patients with hepatic impairment compared with unimpaired patients. No change in VIREAD dosing is required in patients with hepatic impairment.

Assessment of Drug Interactions

At concentrations substantially higher (~300-fold) than those observed in vivo, tenofovir did not inhibit in vitro drug metabolism mediated by any of the following human CYP isoforms: CYP3A4, CYP2D6, CYP2C9, or CYP2E1. However, a small (6%) but statistically significant reduction in metabolism of CYP1A substrate was observed. Based on the results of in vitro experiments and the known elimination pathway of tenofovir, the potential for CYP mediated interactions involving tenofovir with other medicinal products is low [See *Clinical Pharmacology* (12.3)].

VIREAD has been evaluated in healthy volunteers in combination with abacavir, atazanavir, didanosine, efavirenz, emtricitabine, entecavir, indinavir, lamivudine, lopinavir/ritonavir, methadone, nelfinavir, oral contraceptives, ribavirin, saquinavir/ritonavir, and tacrolimus. Tables 10 and 11 summarize pharmacokinetic effects of coadministered drug on tenofovir pharmacokinetics and effects of VIREAD on the pharmacokinetics of coadministered drug.

Table 10 Drug Interactions: Changes in Pharmacokinetic Parameters for Tenofovir* in the Presence of the Coadministered Drug

| Coadministered Drug | Dose of Coadministered Drug (mg) | N | % Change of Tenofovir Pharmacokinetic Parameters [†] (90% CI) | | |
|-----------------------------|------------------------------------|----|---|------------------------|------------------------|
| | | | C _{max} | AUC | C _{min} |
| Abacavir | 300 once | 8 | * | * | NC |
| Atazanavir [‡] | 400 once daily × 14 days | 33 | ↑ 14 (↑ 8 to ↑ 20) | ↑ 24 (↑ 21 to ↑ 28) | ↑ 22 (↑ 15 to ↑ 30) |
| Didanosine (enteric-coated) | 400 once | 25 | * | * | * |
| Didanosine (buffered) | 250 or 400 once daily × 7 days | 14 | * | * | * |
| Efavirenz | 600 once daily × 14 days | 29 | * | * | * |
| Emtricitabine | 200 once daily × 7 days | 17 | * | * | * |
| Entecavir | 1 mg once daily × 10 days | 28 | * | * | * |
| Indinavir | 800 three times daily × 7 days | 13 | ↑ 14 (↓ 3 to ↑ 33) | * | * |
| Lamivudine | 150 twice daily × 7 days | 15 | * | * | * |
| Lopinavir/Ritonavir | 400/100 twice daily × 14 days | 24 | * | ↑ 32 (↑ 25 to ↑ 38) | ↑ 51 (↑ 37 to ↑ 66) |
| Nelfinavir | 1250 twice daily × 14 days | 29 | * | * | * |
| Saquinavir/Ritonavir | 1000/100 twice daily × 14 days | 35 | * | * | ↑ 23 (↑ 16 to ↑ 30) |
| Tacrolimus | 0.05 mg/kg twice daily × 7 days | 21 | ↑ 13 (↑ 1 to ↑ 27) | * | * |

*Patients received VIREAD 300 mg once daily.

†

Increase = ↑; Decrease = ↓; No Effect = *; NC = Not Calculated

‡Reyataz Prescribing Information

Following multiple dosing to HIV- and HBV-negative subjects receiving either chronic methadone maintenance therapy or oral contraceptives, or single doses of ribavirin, steady state tenofovir pharmacokinetics were similar to those observed in previous studies, indicating lack of clinically significant drug interactions between these agents and VIREAD.

Table 11 Drug Interactions: Changes in Pharmacokinetic Parameters for Coadministered Drug in the Presence of VIREAD

| Coadministered Drug | Dose of Coadministered Drug (mg) | N | % Change of Coadministered Drug Pharmacokinetic Parameters* (90% CI) | | |
|----------------------------------|--|----|--|-------------------------------------|-------------------------------------|
| | | | C _{max} | AUC | C _{min} |
| Abacavir | 300 once | 8 | ↑ 12 (↓ 1 to ↑ 26) | * | NA |
| Atazanavir [†] | 400 once daily × 14 days | 34 | ↓ 21 (↓ 27 to ↓ 14) | ↓ 25 (↓ 30 to ↓ 19) | ↓ 40 (↓ 48 to ↓ 32) |
| Atazanavir [†] | Atazanavir/ Ritonavir 300/100 once daily × 42 days | 10 | ↓ 28 (↓ 50 to ↑ 5) | ↓ 25 [‡] (↓ 42 to ↓ 3) | ↓ 23 [‡] (↓ 46 to ↑ 10) |
| Efavirenz | 600 once daily × 14 days | 30 | * | * | * |
| Emtricitabine | 200 once daily × 7 days | 17 | * | * | ↑ 20 (↑ 12 to ↑ 29) |
| Entecavir | 1 mg once daily × 10 days | 28 | * | ↑ 13 (↑ 11 to ↑ 15) | * |
| Indinavir | 800 three times daily × 7 days | 12 | ↓ 11 (↓ 30 to ↑ 12) | * | * |
| Lamivudine | 150 twice daily × 7 days | 15 | ↓ 24 (↓ 34 to ↓ 12) | * | * |
| Lopinavir | Lopinavir/Ritonavir 400/100 twice daily × 14 days | 24 | * | * | * |
| Ritonavir | | | * | * | * |
| Methadone [§] | 40–110 once daily × 14 days [¶] | 13 | * | * | * |
| Nelfinavir | 1250 twice daily × 14 days | 29 | * | * | * |
| M8 metabolite | | | * | * | * |
| Oral Contraceptives [#] | Ethinyl Estradiol/ Norgestimate (Ortho-Tricyclen) once daily × 7 days | 20 | * | * | * |
| Ribavirin | 600 once | 22 | * | * | NA |
| Saquinavir | Saquinavir/Ritonavir 1000/100 twice daily × 14 days | 32 | ↑ 22 (↑ 6 to ↑ 41) | ↑ 29 ^p (↑ 12 to ↑ 48) | ↑ 47 ^p (↑ 23 to ↑ 76) |
| Ritonavir | | | * | * | ↑ 23 (↑ 3 to ↑ 46) |
| Tacrolimus | 0.05 mg/kg twice daily × 7 days | 21 | * | * | * |

*

Increase = ↑; Decrease = ↓; No Effect = ∅; NA = Not Applicable

†Reyataz Prescribing Information

‡In HIV-infected patients, addition of tenofovir DF to atazanavir 300 mg plus ritonavir 100 mg, resulted in AUC and C_{min} values of atazanavir that were 2.3- and 4-fold higher than the respective values observed for atazanavir 400 mg when given alone.

§R-(active), S- and total methadone exposures were equivalent when dosed alone or with VIREAD.

¶Individual subjects were maintained on their stable methadone dose. No pharmacodynamic alterations (opiate toxicity or withdrawal signs or symptoms) were reported.

#Ethinyl estradiol and 17-deacetyl norgestimate (pharmacologically active metabolite) exposures were equivalent when dosed alone or with VIREAD.

‡Increases in AUC and C_{min} are not expected to be clinically relevant; hence no dose adjustments are required when tenofovir DF and ritonavir-boosted saquinavir are coadministered.

Table 12 summarizes the drug interaction between VIREAD and didanosine. Coadministration of VIREAD and didanosine should be undertaken with caution [See *Drug Interactions* (7.1)]. When administered with multiple doses of VIREAD, the C_{max} and AUC of didanosine 400 mg increased significantly. The mechanism of this interaction is unknown. When didanosine 250 mg enteric-coated capsules were administered with VIREAD, systemic exposures to didanosine were similar to those seen with the 400 mg enteric-coated capsules alone under fasted conditions.

Table 12 Drug Interactions: Pharmacokinetic Parameters for Didanosine in the Presence of VIREAD

| Didanosine Dose (mg)/ Method of Administration | VIREAD Method of Administration * | N | % Difference (90% CI) vs. Didanosine 400 mg Alone, Fasted [†] | |
|--|-------------------------------------|----|--|------------------------|
| | | | C _{max} | AUC |
| Buffered tablets | | | | |
| 400 once daily [‡] × 7 days | Fasted 1 hour after didanosine | 14 | ↑ 28 (↑ 11 to ↑ 48) | ↑ 44 (↑ 31 to ↑ 59) |
| Enteric coated capsules | | | | |
| 400 once, fasted | With food, 2 hours after didanosine | 26 | ↑ 48 (↑ 25 to ↑ 76) | ↑ 48 (↑ 31 to ↑ 67) |
| 400 once, with food | Simultaneously with didanosine | 26 | ↑ 64 (↑ 41 to ↑ 89) | ↑ 60 (↑ 44 to ↑ 79) |
| 250 once, fasted | With food, 2 hours after didanosine | 28 | ↓ 10 (↓ 22 to ↑ 3) | * |
| 250 once, fasted | Simultaneously with didanosine | 28 | * | ↑ 14 (0 to ↑ 31) |
| 250 once, with food | Simultaneously with didanosine | 28 | ↓ 29 (↓ 39 to ↓ 18) | ↓ 11 (↓ 23 to ↑ 2) |

*Administration with food was with a light meal (~373 kcal, 20% fat).

†

Increase = ↑; Decrease = ↓; No Effect = ∅

‡Includes 4 subjects weighing <60 kg receiving ddI 250 mg.

12.4 Microbiology

Mechanism of Action

Tenofovir disoproxil fumarate is an acyclic nucleoside phosphonate diester analog of adenosine monophosphate. Tenofovir disoproxil fumarate requires initial diester hydrolysis for conversion to tenofovir and subsequent phosphorylations by cellular enzymes to form tenofovir diphosphate, an obligate chain terminator. Tenofovir diphosphate inhibits the activity of HIV-1 reverse transcriptase and HBV polymerase by competing with the natural substrate deoxyadenosine 5'-triphosphate and, after incorporation into DNA, by DNA chain termination. Tenofovir diphosphate is a weak inhibitor of mammalian DNA polymerases α, β, and mitochondrial DNA polymerase γ.

Activity against HIV

Antiviral Activity

The antiviral activity of tenofovir against laboratory and clinical isolates of HIV-1 was assessed in lymphoblastoid cell lines, primary monocyte/macrophage cells and peripheral blood lymphocytes. The EC₅₀ (50% effective concentration) values for tenofovir were in the range of 0.04 µM to 8.5 µM. In drug combination studies of tenofovir with nucleoside reverse transcriptase inhibitors (abacavir, didanosine, lamivudine, stavudine, zalcitabine, zidovudine), non-nucleoside reverse transcriptase inhibitors (delavirdine, efavirenz, nevirapine), and protease inhibitors (amprenavir, indinavir, nelfinavir, ritonavir, saquinavir), additive to synergistic effects were observed. Tenofovir displayed antiviral activity in cell culture against HIV-1 clades A, B, C, D, E, F, G, and O (EC₅₀ values ranged from 0.5 µM to 2.2 µM) and strain specific activity against HIV-2 (EC₅₀ values ranged from 1.6 µM to 5.5 µM).

Resistance

HIV-1 isolates with reduced susceptibility to tenofovir have been selected in cell culture. These viruses expressed a K65R substitution in reverse transcriptase and showed a 2–4 fold reduction in susceptibility to tenofovir.

In Study 903 of treatment-naïve patients (VIREAD + lamivudine + efavirenz versus stavudine + lamivudine + efavirenz) [See *Clinical Studies (14.1)*], genotypic analyses of isolates from patients with virologic failure through Week 144 showed development of efavirenz and lamivudine resistance-associated substitutions to occur most frequently and with no difference between the treatment arms. The K65R substitution occurred in 8/47 (17%) analyzed patient isolates on the VIREAD arm and in 2/49 (4%) analyzed patient isolates on the stavudine arm. Of the 8 patients whose virus developed K65R in the VIREAD arm through 144 weeks, 7 of these occurred in the first 48 weeks of treatment and one at Week 96. Other substitutions resulting in resistance to VIREAD were not identified in this study.

In Study 934 of treatment-naïve patients (VIREAD + EMTRIVA + efavirenz versus zidovudine (AZT)/lamivudine (3TC) + efavirenz) [See *Clinical Studies (14.1)*], genotypic analysis performed on HIV-1 isolates from all confirmed virologic failure patients with >400 copies/mL of HIV-1 RNA at Week 144 or early discontinuation showed development of efavirenz resistance-associated substitutions occurred most frequently and was similar between the two treatment arms. The M184V substitution, associated with resistance to EMTRIVA and lamivudine, was observed in 2/19 analyzed patient isolates in the VIREAD + EMTRIVA group and in 10/29 analyzed patient isolates in the zidovudine/lamivudine group. Through 144 weeks of Study 934, no patients have developed a detectable K65R substitution in their HIV-1 as analyzed through standard genotypic analysis.

Cross Resistance

Cross-resistance among certain reverse transcriptase inhibitors has been recognized. The K65R substitution selected by tenofovir is also selected in some HIV-1 infected subjects treated with abacavir, didanosine, or zalcitabine. HIV-1 isolates with this mutation also show reduced susceptibility to emtricitabine and lamivudine. Therefore, cross-resistance among these drugs may occur in patients whose virus harbors the K65R substitution. HIV-1 isolates from patients (N=20) whose HIV-1 expressed a mean of 3 zidovudine-associated reverse transcriptase substitutions (M41L, D67N, K70R, L210W, T215Y/F, or K219Q/E/N), showed a 3.1-fold decrease in the susceptibility to tenofovir. Multinucleoside resistant HIV-1 with a T69S double insertion substitution in the reverse transcriptase showed reduced susceptibility to tenofovir.

In Studies 902 and 907 conducted in treatment-experienced patients (VIREAD + Standard Background Therapy (SBT) compared to Placebo + SBT) [See *Clinical Studies (14.1)*], 14/304 (5%) of the VIREAD-treated patients with virologic failure through Week 96 had >1.4-fold (median 2.7-fold) reduced susceptibility to tenofovir. Genotypic analysis of the baseline and failure isolates showed the development of the K65R substitution in the HIV-1 reverse transcriptase gene.

The virologic response to VIREAD therapy has been evaluated with respect to baseline viral genotype (N=222) in treatment-experienced patients participating in Studies 902 and 907.

In these clinical studies, 94% of the participants evaluated had baseline HIV-1 isolates expressing at least one NRTI mutation. These included resistance substitutions associated with zidovudine (M41L, D67N, K70R, L210W, T215Y/F, or K219Q/E/N), the abacavir/emtricitabine/lamivudine resistance-associated substitution (M184V), and others. In addition the majority of participants evaluated had substitutions associated with either PI or NNRTI use. Virologic responses for patients in the genotype substudy were similar to the overall study results.

Several exploratory analyses were conducted to evaluate the effect of specific substitutions and substitutional patterns on virologic outcome. Because of the large number of potential comparisons, statistical testing was not conducted. Varying degrees of cross-resistance of VIREAD to pre-existing zidovudine resistance-associated substitutions were observed and appeared to depend on the number of specific substitutions. VIREAD-treated patients whose HIV-1 expressed 3 or more zidovudine resistance-associated substitutions that included either the M41L or L210W reverse transcriptase substitution showed reduced responses to VIREAD

therapy; however, these responses were still improved compared with placebo. The presence of the D67N, K70R, T215Y/F, or K219Q/E/N substitution did not appear to affect responses to VIREAD therapy.

In the protocol defined analyses, virologic response to VIREAD was not reduced in patients with HIV-1 that expressed the abacavir/emtricitabine/lamivudine resistance-associated M184V substitution. In the presence of zidovudine resistance-associated substitutions, the M184V substitution did not affect the mean HIV-1 RNA responses to VIREAD treatment. HIV-1 RNA responses among these patients were durable through Week 48.

Studies 902 and 907 Phenotypic Analyses

The virologic response to VIREAD therapy has been evaluated with respect to baseline phenotype (N=100) in treatment-experienced patients participating in two controlled trials. Phenotypic analysis of baseline HIV-1 from patients in these studies demonstrated a correlation between baseline susceptibility to VIREAD and response to VIREAD therapy. Table 13 summarizes the HIV-1 RNA response by baseline VIREAD susceptibility.

Table 13 HIV-1 RNA Response at Week 24 by Baseline VIREAD Susceptibility (Intent-To-Treat)*

| Baseline VIREAD Susceptibility [†] | Change in HIV-1 RNA [‡] (N) |
|---|--------------------------------------|
| <1 | -0.74 (35) |
| >1 and ≤3 | -0.56 (49) |
| >3 and ≤4 | -0.3 (7) |
| >4 | -0.12 (9) |

*Tenofovir susceptibility was determined by recombinant phenotypic Antivirogram assay (Virco).

[†]Fold change in susceptibility from wild-type.

[‡]Average HIV-1 RNA change from baseline through Week 24 (DAVG₂₄) in log₁₀ copies/mL.

Activity against HBV

Antiviral Activity

The antiviral activity of tenofovir against HBV was assessed in the HepG2 2.2.15 cell line. The EC₅₀ values for tenofovir ranged from 0.14 to 1.5 μM, with CC₅₀ (50% cytotoxicity concentration) values >100 μM. In cell culture combination antiviral activity studies of tenofovir with the nucleoside anti-HBV reverse transcriptase inhibitors emtricitabine, entecavir, lamivudine and telbivudine, no antagonistic activity was observed.

Resistance

Out of 426 HBeAg negative and HBeAg positive patients, 39 patients had serum HBV DNA >400 copies/mL at Week 48. Genotypic data from paired baseline and on treatment isolates were available for 28 of the 39 patients. No specific amino acid substitutions occurred in these subjects' isolates at sufficient frequency to establish an association with tenofovir resistance.

Cross Resistance

Cross-resistance has been observed among HBV reverse transcriptase inhibitors.

In cell based assays, HBV strains expressing the rtV173L, rtL180M, and rtM204I/V substitutions associated with resistance to lamivudine and telbivudine showed a susceptibility to tenofovir ranging from 0.7 to 3.4-fold that of wild type virus. The rtL180M and rtM204I/V double substitutions conferred 3.4-fold reduced susceptibility to tenofovir.

HBV strains expressing the rtL180M, rtT184G, rtS202G/I, rtM204V, and rtM250V substitutions associated with resistance to entecavir showed a susceptibility to tenofovir ranging from 0.6 to 6.9-fold that of wild type virus. An HBV strain expressing rtL180M, rtT184G, rtS202I and rtM204V together had a 6.9-fold reduction in susceptibility to tenofovir.

HBV strains expressing the adefovir-associated resistance substitutions rtA181V and/or rtN236T showed reductions in susceptibility to tenofovir ranging from 2.9 to 10-fold that of wild type virus.

Strains containing the rtA181T substitution showed changes in susceptibility to tenofovir ranging from 0.9 to 1.5-fold that of wild type virus.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term oral carcinogenicity studies of tenofovir disoproxil fumarate in mice and rats were carried out at exposures up to approximately 16 times (mice) and 5 times (rats) those observed in humans at the therapeutic dose for HIV-1 infection. At the high dose in female mice, liver adenomas were increased at exposures 16 times that in humans. In rats, the study was negative for carcinogenic findings at exposures up to 5 times that observed in humans at the therapeutic dose.

Tenofovir disoproxil fumarate was mutagenic in the in vitro mouse lymphoma assay and negative in an in vitro bacterial mutagenicity test (Ames test). In an in vivo mouse micronucleus assay, tenofovir disoproxil fumarate was negative when administered to male mice. There were no effects on fertility, mating performance or early embryonic development when tenofovir disoproxil fumarate was administered to male rats at a dose equivalent to 10 times the human dose based on body surface area comparisons for 28 days prior to mating and to female rats for 15 days prior to mating through day seven of gestation. There was, however, an alteration of the estrous cycle in female rats.

13.2 Animal Toxicology and/or Pharmacology

Tenofovir and tenofovir disoproxil fumarate administered in toxicology studies to rats, dogs, and monkeys at exposures (based on AUCs) greater than or equal to 6 fold those observed in humans caused bone toxicity. In monkeys the bone toxicity was diagnosed as osteomalacia. Osteomalacia observed in monkeys appeared to be reversible upon dose reduction or discontinuation of tenofovir. In rats and dogs, the bone toxicity manifested as reduced bone mineral density. The mechanism(s) underlying bone toxicity is unknown. Evidence of renal toxicity was noted in 4 animal species. Increases in serum creatinine, BUN, glycosuria, proteinuria, phosphaturia, and/or calciuria and decreases in serum phosphate were observed to varying degrees in these animals. These toxicities were noted at exposures (based on AUCs) 2–20 times higher than those observed in humans. The relationship of the renal abnormalities, particularly the phosphaturia, to the bone toxicity is not known.

14 CLINICAL STUDIES

14.1 Clinical Efficacy in Patients with HIV-1 Infection

Treatment-Naïve Patients

Study 903

Data through 144 weeks are reported for Study 903, a double-blind, active-controlled multicenter study comparing VIREAD (300 mg once daily) administered in combination with lamivudine and efavirenz versus stavudine (d4T), lamivudine, and efavirenz in 600 antiretroviral-naïve patients. Patients had a mean age of 36 years (range 18–64), 74% were male, 64% were Caucasian and 20% were Black. The mean baseline CD4⁺ cell count was 279 cells/mm³ (range 3–956) and median baseline plasma HIV-1 RNA was 77,600 copies/mL (range 417–5,130,000). Patients were stratified by baseline HIV-1 RNA and CD4⁺ cell count. Forty-three percent of patients had baseline viral loads >100,000 copies/mL and 39% had CD4⁺ cell counts <200 cells/mm³. Treatment outcomes through 48 and 144 weeks are presented in Table 14.

Table 14 Outcomes of Randomized Treatment at Week 48 and 144 (Study 903)

| Outcomes | At Week 48 | | At Week 144 | |
|---|-------------------------------|----------------------------|-------------------------------|----------------------------|
| | VIREAD+3TC +EFV (N=299) | d4T+3TC +EFV (N=301) | VIREAD+3TC +EFV (N=299) | d4T+3TC +EFV (N=301) |
| Responder [*] | 79% | 82% | 68% | 62% |
| Virologic failure [†] | 6% | 4% | 10% | 8% |
| Rebound | 5% | 3% | 8% | 7% |
| Never suppressed | 0% | 1% | 0% | 0% |
| Added an antiretroviral agent | 1% | 1% | 2% | 1% |
| Death | <1% | 1% | <1% | 2% |
| Discontinued due to adverse event | 6% | 6% | 8% | 13% |
| Discontinued for other reasons [‡] | 8% | 7% | 14% | 15% |

*Patients achieved and maintained confirmed HIV-1 RNA <400 copies/mL through Week 48 and 144.

†Includes confirmed viral rebound and failure to achieve confirmed <400 copies/mL through Week 48 and 144.

‡Includes lost to follow-up, patient's withdrawal, noncompliance, protocol violation and other reasons.

Achievement of plasma HIV-1 RNA concentrations of less than 400 copies/mL at Week 144 was similar between the two treatment groups for the population stratified at baseline on the basis of HIV-1 RNA concentration ($>$ or $\leq 100,000$ copies/mL) and CD4⁺ cell count ($<$ or ≥ 200 cells/mm³). Through 144 weeks of therapy, 62% and 58% of patients in the VIREAD and stavudine arms, respectively achieved and maintained confirmed HIV-1 RNA <50 copies/mL. The mean increase from baseline in CD4⁺ cell count was 263 cells/mm³ for the VIREAD arm and 283 cells/mm³ for the stavudine arm.

Through 144 weeks, 11 patients in the VIREAD group and 9 patients in the stavudine group experienced a new CDC Class C event.

Study 934

Data through 144 weeks are reported for Study 934, a randomized, open-label, active-controlled multicenter study comparing emtricitabine + VIREAD administered in combination with efavirenz versus zidovudine/lamivudine fixed-dose combination administered in combination with efavirenz in 511 antiretroviral-naïve patients. From Weeks 96 to 144 of the study, patients received a fixed-dose combination of emtricitabine and tenofovir DF with efavirenz in place of emtricitabine + VIREAD with efavirenz. Patients had a mean age of 38 years (range 18–80), 86% were male, 59% were Caucasian and 23% were Black. The mean baseline CD4⁺ cell count was 245 cells/mm³ (range 2–1191) and median baseline plasma HIV-1 RNA was 5.01 log₁₀ copies/mL (range 3.56–6.54). Patients were stratified by baseline CD4⁺ cell count ($<$ or ≥ 200 cells/mm³); 41% had CD4⁺ cell counts <200 cells/mm³ and 51% of patients had baseline viral loads $>100,000$ copies/mL. Treatment outcomes through 48 and 144 weeks for those patients who did not have efavirenz resistance at baseline are presented in Table 15.

Table 15 Outcomes of Randomized Treatment at Week 48 and 144 (Study 934)

| Outcomes | At Week 48 | | At Week 144 | |
|---|-----------------------------------|----------------------------|------------------------------------|-----------------------------|
| | FTC +VIREAD +EFV (N=244) | AZT/3TC +EFV (N=243) | FTC +VIREAD +EFV (N=227)* | AZT/3TC +EFV (N=229)* |
| Responder [†] | 84% | 73% | 71% | 58% |
| Virologic failure [‡] | 2% | 4% | 3% | 6% |
| Rebound | 1% | 3% | 2% | 5% |
| Never suppressed | 0% | 0% | 0% | 0% |
| Change in antiretroviral regimen | 1% | 1% | 1% | 1% |
| Death | $<1\%$ | 1% | 1% | 1% |
| Discontinued due to adverse event | 4% | 9% | 5% | 12% |
| Discontinued for other reasons [§] | 10% | 14% | 20% | 22% |

*Patients who were responders at Week 48 or Week 96 (HIV-1 RNA <400 copies/mL) but did not consent to continue study after Week 48 or Week 96 were excluded from analysis.

[†]Patients achieved and maintained confirmed HIV-1 RNA <400 copies/mL through Weeks 48 and 144.

[‡]Includes confirmed viral rebound and failure to achieve confirmed <400 copies/mL through Weeks 48 and 144.

[§]Includes lost to follow-up, patient withdrawal, noncompliance, protocol violation and other reasons.

Through Week 48, 84% and 73% of patients in the emtricitabine + VIREAD group and the zidovudine/lamivudine group, respectively, achieved and maintained HIV-1 RNA <400 copies/mL (71% and 58% through Week 144). The difference in the proportion of patients who achieved and maintained HIV-1 RNA <400 copies/mL through 48 weeks largely results from the higher number of discontinuations due to adverse events and other reasons in the zidovudine/lamivudine group in this open-label study. In addition, 80% and 70% of patients in the emtricitabine + VIREAD group and the zidovudine/lamivudine group, respectively, achieved and maintained HIV-1 RNA <50 copies/mL through Week 48 (64% and 56% through Week 144). The mean increase from baseline in CD4⁺ cell count was 190 cells/mm³ in the EMTRIVA + VIREAD group and 158 cells/mm³ in the zidovudine/lamivudine group at Week 48 (312 and 271 cells/mm³ at Week 144).

Through 48 weeks, 7 patients in the emtricitabine + VIREAD group and 5 patients in the zidovudine/lamivudine group experienced a new CDC Class C event (10 and 6 patients through 144 weeks).

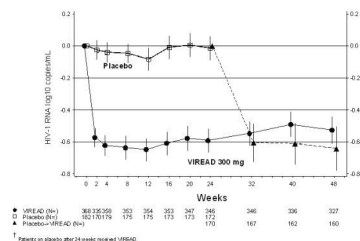
Treatment-Experienced Patients

Study 907

Study 907 was a 24-week, double-blind placebo-controlled multicenter study of VIREAD added to a stable background regimen of antiretroviral agents in 550 treatment-experienced patients. After 24 weeks of blinded study treatment, all patients continuing on study were offered open-label VIREAD for an additional 24 weeks. Patients had a mean baseline CD4⁺ cell count of 427 cells/mm³ (range 23–1385), median baseline plasma HIV-1 RNA of 2340 (range 50–75,000) copies/mL, and mean duration of prior HIV-1 treatment was 5.4 years. Mean age of the patients was 42 years, 85% were male and 69% were Caucasian, 17% Black and 12% Hispanic.

Changes from baseline in log₁₀ copies/mL plasma HIV-1 RNA levels over time up to Week 48 are presented below in Figure 1.

Figure 1 Mean Change from Baseline in Plasma HIV-1 RNA (log₁₀ copies/mL) Through Week 48 (Study 907; All Available Data)[†]



The percent of patients with HIV-1 RNA <400 copies/mL and outcomes of patients through 48 weeks are summarized in Table 16.

Table 16 Outcomes of Randomized Treatment (Study 907)

| Outcomes | 0–24 weeks | | 0–48 weeks | 24–48 weeks |
|---|-------------------|--------------------|-------------------|--|
| | VIREAD (N=368) | Placebo (N=182) | VIREAD (N=368) | Placebo Crossover to VIREAD (N=170) |
| HIV-1 RNA <400 copies/mL [*] | 40% | 11% | 28% | 30% |
| Virologic failure [†] | 53% | 84% | 61% | 64% |
| Discontinued due to adverse event | 3% | 3% | 5% | 5% |
| Discontinued for other reasons [‡] | 3% | 3% | 5% | 1% |

*Patients with HIV-1 RNA <400 copies/mL and no prior study drug discontinuation at Week 24 and 48 respectively.

†Patients with HIV-1 RNA ≥400 copies/mL efficacy failure or missing HIV-1 RNA at Week 24 and 48 respectively.

‡Includes lost to follow-up, patient withdrawal, noncompliance, protocol violation and other reasons.

At 24 weeks of therapy, there was a higher proportion of patients in the VIREAD arm compared to the placebo arm with HIV-1 RNA <50 copies/mL (19% and 1%, respectively). Mean change in absolute CD4⁺ cell counts by Week 24 was +11 cells/mm³ for the VIREAD group and -5 cells/mm³ for the placebo group. Mean change in absolute CD4⁺ cell counts by Week 48 was +4 cells/mm³ for the VIREAD group.

Through Week 24, one patient in the VIREAD group and no patients in the placebo arm experienced a new CDC Class C event.

14.2 Clinical Efficacy in Patients with Chronic Hepatitis B

HBeAg-Negative Chronic Hepatitis B

Study 0102 was a Phase 3, randomized, double-blind, active-controlled study of VIREAD 300 mg compared to HEPSEARA 10 mg in 375 HBeAg- (anti-HBe+) patients with compensated liver function, the majority of whom were nucleoside-naïve. The mean age of patients was 44 years, 77% were male, 25% were Asian, 65% were Caucasian, 17% had previously received alpha-interferon therapy and 18% were nucleoside-experienced (16% had prior lamivudine experience). At baseline, patients had a mean Knodell necroinflammatory score of 7.8; mean plasma HBV DNA was 6.9 log₁₀ copies/mL; and mean serum ALT was 140 U/L.

HBeAg-Positive Chronic Hepatitis B

Study 0103 was a Phase 3, randomized, double-blind, active-controlled study of VIREAD 300 mg compared to HEPSEARA 10 mg in 266 HBeAg+ nucleoside-naïve patients with compensated liver function. The mean age of patients was 34 years, 69% were male, 36% were Asian, 52% were Caucasian, 16% had previously received alpha-interferon therapy, and <5% were nucleoside experienced. At baseline, patients had a mean Knodell necroinflammatory score of 8.4; mean plasma HBV DNA was 8.7 log₁₀ copies/mL; and mean serum ALT was 147 U/L.

The primary data analysis was conducted after all patients reached 48 weeks of treatment and results are summarized below.

The primary efficacy endpoint in both studies was complete response to treatment defined as HBV DNA <400 copies/mL and Knodell necroinflammatory score improvement of at least 2 points, without worsening in Knodell fibrosis at Week 48 (Table 17).

Table 17 Histological, Virological, Biochemical, and Serological Response at Week 48

| | 0102 (HBeAg-) | | 0103 (HBeAg+) | |
|--|---------------------------|----------------------------|---------------------------|---------------------------|
| | VIREAD (N=250) | HEPSERA (N=125) | VIREAD (N=176) | HEPSERA (N=90) |
| Complete Response | 71% | 49% | 67% | 12% |
| Histology | | | | |
| Histological Response* | 72% | 69% | 74% | 68% |
| HBV DNA <400 copies/mL (<69 IU/mL) | 93% | 63% | 76% | 13% |
| ALT Normalized ALT† | 76% | 77% | 68% | 54% |
| Serology HBeAg Loss/Seroconversion | NA‡ | NA‡ | 20%/19% | 16%/16% |
| HBsAg Loss/Seroconversion | 0/0 | 0/0 | 3%/1% | 0/0 |

*Knodell necroinflammatory score improvement of at least 2 points without worsening in Knodell fibrosis.

†The population used for analysis of ALT normalization included only patients with ALT above ULN at baseline.

‡NA = Not Applicable

A small proportion of nucleoside-experienced patients received VIREAD in the clinical trials: 43 patients in Study 0102 and 8 patients in Study 0103. Across both studies, 5 patients had HBV containing lamivudine-resistance associated substitutions at baseline. The numbers of patients in these subgroups were too small to establish efficacy.

16 HOW SUPPLIED/STORAGE AND HANDLING

The almond-shaped, light blue, film-coated tablets contain 300 mg of tenofovir disoproxil fumarate, which is equivalent to 245 mg of tenofovir disoproxil, are debossed with "GILEAD" and "4331" on one side and with "300" on the other side, and are available in unit of use bottles (containing a desiccant [silica gel canister or sachet] and closed with a child-resistant closure) of:

- 30 tablets (NDC 61958-0401-1)

Store at 25 °C (77 °F), excursions permitted to 15–30 °C (59–86 °F) (see USP Controlled Room Temperature).

Do not use if seal over bottle opening is broken or missing.

17 PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling (17.2)

17.1 Information for Patients

Patients should be advised that:

- VIREAD is not a cure for HIV-1 infection and patients may continue to experience illnesses associated with HIV-1 infection, including opportunistic infections. Patients should remain under the care of a physician when using VIREAD.
- The use of VIREAD has not been shown to reduce the risk of transmission of HIV-1 or HBV to others through sexual contact or blood contamination.
- The long term effects of VIREAD are unknown.
- VIREAD Tablets are for oral ingestion only.
- VIREAD should not be discontinued without first informing their physician.
- If you have HIV-1 infection, with or without HBV coinfection, it is important to take VIREAD with combination therapy.
- It is important to take VIREAD on a regular dosing schedule and to avoid missing doses.

- Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported. Treatment with VIREAD should be suspended in any patient who develops clinical symptoms suggestive of lactic acidosis or pronounced hepatotoxicity (including nausea, vomiting, unusual or unexpected stomach discomfort, and weakness) [*See Warnings and Precautions (5.1)*].
- Patients with HIV-1 should be tested for Hepatitis B virus (HBV) before initiating antiretroviral therapy [*See Warnings and Precautions (5.5)*].
- Severe acute exacerbations of hepatitis have been reported in patients who are infected with HBV or coinfect with HBV and HIV-1 and have discontinued VIREAD [*See Warnings and Precautions (5.2)*].
- In patients with chronic hepatitis B, it is important to obtain HIV antibody testing prior to initiating VIREAD [*See Warnings and Precautions (5.5)*].
- Renal impairment, including cases of acute renal failure and Fanconi syndrome, has been reported. VIREAD should be avoided with concurrent or recent use of a nephrotoxic agent [*See Warnings and Precautions (5.3)*]. Dosing interval of VIREAD may need adjustment in patients with renal impairment [*See Dosage and Administration (2.2)*].
- VIREAD should not be coadministered with the fixed-dose combination products TRUVADA and ATRIPLA since it is a component of these products [*See Warnings and Precautions (5.4)*].
- VIREAD should not be administered in combination with HEPSERA [*See Warnings and Precautions (5.4)*].
- Decreases in bone mineral density have been observed with the use of VIREAD in patients with HIV. Bone mineral density monitoring should be considered in patients who have a history of pathologic bone fracture or at risk for osteopenia [*See Warnings and Precautions (5.6)*].
- In the treatment of chronic hepatitis B, the optimal duration of treatment is unknown. The relationship between response and long-term prevention of outcomes such as hepatocellular carcinoma is not known.

17.2 FDA-Approved Patient Labeling

VIREAD® (VEER ee ad) Tablets

Generic Name: tenofovir disoproxil fumarate (te NOE' fo veer dye soe PROX il FYOU-mar-ate)

Read this leaflet carefully before you start taking VIREAD. Also, read it each time you get your VIREAD prescription refilled, in case something has changed. This information does not take the place of talking with your healthcare provider when you start this medicine and at check ups. You should stay under a healthcare provider's care when taking VIREAD. Do not change or stop your medicine without first talking with your healthcare provider. Talk to your healthcare provider if you have any questions about VIREAD.

What is VIREAD and how does it work?

VIREAD is a type of medicine called a nucleotide analog reverse transcriptase and HBV polymerase inhibitor (NRTI).

Use in the Treatment of HIV-1 Infection:

VIREAD is a treatment for Human Immunodeficiency Virus (HIV) infection in adults age 18 years and older. VIREAD is always used in combination with other anti-HIV-1 medicines to treat people with HIV-1 infection.

HIV infection destroys CD4⁺ T cells, which are important to the immune system. After a large number of T cells are destroyed, acquired immune deficiency syndrome (AIDS) develops.

VIREAD helps to block HIV-1 reverse transcriptase, a chemical in your body (enzyme) that is needed for HIV-1 to multiply.

VIREAD lowers the amount of HIV-1 in the blood (called viral load) and may help to increase the number of T cells (called CD4⁺ cells). Lowering the amount of HIV-1 in the blood lowers the chance of death or infections that happen when your immune system is weak (opportunistic infections).

Use in the Treatment of Chronic Hepatitis B:

VIREAD is also used to treat chronic hepatitis B (an infection with hepatitis B virus [HBV]) in adults age 18 years and older.

VIREAD works by interfering with the normal working of an enzyme (HBV DNA polymerase) that is essential for the HBV virus to reproduce itself. VIREAD may help lower the amount of hepatitis B virus in your body by lowering the ability of the virus to multiply and infect new liver cells.

Does VIREAD cure HIV-1 or AIDS?

VIREAD does not cure HIV-1 infection or AIDS. The long-term effects of VIREAD are not known at this time. People taking VIREAD may still get opportunistic infections or other conditions that happen with HIV-1 infection. Opportunistic infections are infections that develop because the immune system is weak. Some of these conditions are pneumonia, herpes virus infections, and *Mycobacterium avium* complex (MAC) infections.

We do not know how long VIREAD may help your hepatitis. Sometimes viruses change in your body and medicines no longer work. This is called drug resistance.

We do not know if VIREAD will reduce your chances of getting liver cancer from chronic hepatitis B.

Does VIREAD reduce the risk of passing HIV-1 or HBV to others?

VIREAD does not reduce the risk of passing HIV-1 or HBV to others through sexual contact or blood contamination. Continue to practice safe sex and do not use or share dirty needles.

Who should not take VIREAD?

Together with your healthcare provider, you need to decide whether VIREAD is right for you.

Do not take VIREAD if

- you are allergic to VIREAD or any of its ingredients
- you are already taking TRUVADA[®] or ATRIPLA[®] because VIREAD is one of the active ingredients in TRUVADA and ATRIPLA
- you have not already discontinued treatment with HEPSERA[®]

What should I tell my healthcare provider before taking VIREAD?

Tell your healthcare provider

- *If you are pregnant or planning to become pregnant:* The effects of VIREAD on pregnant women or their unborn babies are not known.
- *If you are breast-feeding:* Do not breast-feed if you are taking VIREAD. Do not breast-feed if you have HIV. If you are a woman who has or will have a baby, talk with your healthcare provider about the best way to feed your baby. If your baby does not already have HIV, there is a chance that the baby can get HIV through breast-feeding.
- **If you have kidney or bone problems**
- **If you have liver problems including Hepatitis B Virus infection**
- **If you have HIV-1 Infection**
- **Tell your healthcare provider about all your medical conditions**

TELL YOUR HEALTHCARE PROVIDER ABOUT ALL THE MEDICINES YOU TAKE, INCLUDING PRESCRIPTION AND NON-PRESCRIPTION MEDICINES AND DIETARY SUPPLEMENTS. ESPECIALLY TELL YOUR HEALTHCARE PROVIDER IF YOU TAKE:

- VIDEX, VIDEX EC (DIDANOSINE). VIREAD MAY INCREASE THE AMOUNT OF VIDEX IN YOUR BLOOD. YOU MAY NEED TO BE FOLLOWED MORE CAREFULLY IF YOU ARE TAKING VIDEX AND VIREAD TOGETHER. IF YOU ARE TAKING VIDEX AND VIREAD TOGETHER YOUR HEALTHCARE PROVIDER MAY NEED TO REDUCE YOUR DOSE OF VIDEX.
- REYATAZ (ATAZANAVIR SULFATE) OR KALETRA (LOPINAVIR/RITONAVIR). THESE MEDICINES MAY INCREASE THE AMOUNT OF VIREAD IN YOUR BLOOD, WHICH COULD RESULT IN MORE SIDE EFFECTS. YOU MAY NEED TO BE FOLLOWED MORE CAREFULLY IF YOU ARE TAKING VIREAD AND REYATAZ OR KALETRA TOGETHER. VIREAD MAY DECREASE THE AMOUNT OF REYATAZ IN YOUR BLOOD. IF YOU ARE TAKING VIREAD AND REYATAZ TOGETHER YOU SHOULD ALSO BE TAKING NORVIR (RITONAVIR).

IT IS A GOOD IDEA TO KEEP A COMPLETE LIST OF ALL THE MEDICINES THAT YOU TAKE. MAKE A NEW LIST WHEN MEDICINES ARE ADDED OR STOPPED. GIVE COPIES OF THIS LIST TO ALL OF YOUR HEALTHCARE PROVIDERS **EVERY** TIME YOU VISIT YOUR HEALTHCARE PROVIDER OR FILL A PRESCRIPTION.

How should I take VIREAD?

- Stay under a healthcare provider's care when taking VIREAD. Do not change your treatment or stop treatment without first talking with your healthcare provider.
- Take VIREAD exactly as your healthcare provider prescribed it. Follow the directions from your healthcare provider, exactly as written on the label. Set up a dosing schedule and follow it carefully.
- If you are taking VIREAD to treat your HIV or if you have HIV and HBV co-infection and are taking VIREAD, always take VIREAD in combination with other anti-HIV medicines. VIREAD and other products like VIREAD may be less likely to work in the future if you are not taking VIREAD with other anti-HIV medicines because you may develop resistance to those medicines.
- Talk to your doctor about taking an HIV test before you start treatment with VIREAD for chronic hepatitis B.
- The usual dose of VIREAD is 1 tablet once a day. If you have kidney problems, your healthcare provider may recommend that you take VIREAD less frequently.

- VIREAD may be taken with or without a meal.
- When your VIREAD supply starts to run low, get more from your healthcare provider or pharmacy. This is very important because the amount of virus in your blood may increase if the medicine is stopped for even a short time. The virus may develop resistance to VIREAD and become harder to treat.
- Only take medicine that has been prescribed specifically for you. Do not give VIREAD to others or take medicine prescribed for someone else.

What should I do if I miss a dose of VIREAD?

It is important that you do not miss any doses. If you miss a dose of VIREAD, take it as soon as possible and then take your next scheduled dose at its regular time. If it is almost time for your next dose, do not take the missed dose. Wait and take the next dose at the regular time. Do not double the next dose.

What happens if I take too much VIREAD?

If you suspect that you took more than the prescribed dose of VIREAD, contact your local poison control center or emergency room right away.

As with all medicines, VIREAD should be kept out of reach of children.

What should I avoid while taking VIREAD?

- Do not breast-feed. See "What should I tell my healthcare provider before taking VIREAD?"

What are the possible side effects of VIREAD?

- Clinical studies in patients with HIV-1: The most common side effects of VIREAD are: rash, headache, pain, diarrhea, depression, weakness, and nausea. Less common side effects include vomiting, dizziness, and intestinal gas.
Clinical studies in patients with chronic hepatitis B: The most common side effect of VIREAD is nausea. Less common side effects include abdominal pain, diarrhea, headache, dizziness, fatigue, nasopharyngitis, back pain, and skin rash.
- Marketing experience: Other side effects reported since VIREAD has been marketed include: lactic acidosis, kidney problems (including decline or failure of kidney function), inflammation of the pancreas, inflammation of the liver, allergic reaction, shortness of breath, stomach pain, and high volume of urine and thirst caused by kidney problems. Muscle pain and muscle weakness, bone pain, and softening of the bone (which may contribute to fractures) as a consequence of kidney problems have been reported.
- Some patients treated with VIREAD have had kidney problems. If you have had kidney problems in the past or need to take another drug that can cause kidney problems, your healthcare provider may need to perform additional blood tests.
- Laboratory tests show changes in the bones of patients treated with VIREAD. If you have had bone problems in the past, your healthcare provider may need to perform additional tests or may suggest additional medication. Additionally, bone pain and softening of the bone (which may contribute to fractures) may occur as a consequence of kidney problems.
- Some patients taking antiviral drugs like VIREAD have developed a condition called lactic acidosis (a buildup in the blood of lactic acid, the same substance that causes your muscles to burn during heavy exercise). Symptoms of lactic acidosis include nausea, vomiting, unusual or unexpected stomach discomfort, and weakness. If you notice these symptoms or if your medical condition changes suddenly, call your healthcare provider right away.
- Changes in body fat have been seen in some patients taking anti-HIV-1 medicine. These changes may include increased amount of fat in the upper back and neck ("buffalo hump"), breast, and around the main part of your body (trunk). Loss of fat from the legs, arms and face may also happen. The cause and long term health effects of these conditions are not known at this time.
- In some patients with advanced HIV infection (AIDS), signs and symptoms of inflammation from previous infections may occur soon after anti-HIV treatment is started. It is believed that these symptoms are due to an improvement in the body's immune response, enabling the body to fight infections that may have been present with no obvious symptoms. If you notice any symptoms of infection, please inform your doctor immediately.
- If you have HBV infection or HIV and HBV infection together, you may have a "flare-up" of Hepatitis B, in which the disease suddenly returns in a worse way than before if you stop taking VIREAD. Do not stop taking VIREAD without your doctor's advice. After stopping VIREAD, tell your doctor immediately about any new, unusual, or worsening symptoms that you notice after stopping treatment. After you stop taking VIREAD, your doctor will still need to check your health and take blood tests to check your liver for several months.
- There have been other side effects in patients taking VIREAD. However, these side effects may have been due to other medicines that patients were taking or to the illness itself. Some of these side effects can be serious.

- This list of side effects is **not** complete. If you have questions about side effects, ask your healthcare provider. You should report any new or continuing symptoms to your healthcare provider right away. Your healthcare provider may be able to help you manage these side effects.

How do I store VIREAD?

- Keep VIREAD and all other medications out of reach of children.
- Store VIREAD at room temperature 77 °F (25 °C). It should remain stable until the expiration date printed on the label.
- Do not keep your medicine in places that are too hot or cold.
- Do not keep medicine that is out of date or that you no longer need. If you throw any medicines away make sure that children will not find them.

General advice about prescription medicines:

TALK TO YOUR HEALTHCARE PROVIDER IF YOU HAVE ANY QUESTIONS ABOUT THIS MEDICINE OR YOUR CONDITION. MEDICINES ARE SOMETIMES PRESCRIBED FOR PURPOSES OTHER THAN THOSE LISTED IN A PATIENT INFORMATION LEAFLET. IF YOU HAVE ANY CONCERNS ABOUT THIS MEDICINE, ASK YOUR HEALTHCARE PROVIDER. YOUR HEALTHCARE PROVIDER OR PHARMACIST CAN GIVE YOU INFORMATION ABOUT THIS MEDICINE THAT WAS WRITTEN FOR HEALTH CARE PROFESSIONALS. DO NOT USE THIS MEDICINE FOR A CONDITION FOR WHICH IT WAS NOT PRESCRIBED. DO NOT SHARE THIS MEDICINE WITH OTHER PEOPLE. DO NOT USE IF SEAL OVER BOTTLE OPENING IS BROKEN OR MISSING.

What are the ingredients of VIREAD?

Active Ingredient: tenofovir disoproxil fumarate

Inactive Ingredients: croscarmellose sodium, lactose monohydrate, magnesium stearate, microcrystalline cellulose, and pregelatinized starch. The tablets are coated with Opadry II Y-30-10671-A, which contains FD&C blue #2 aluminum lake, hydroxypropyl methylcellulose 2910, lactose monohydrate, titanium dioxide, and triacetin.

November 2008

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PRINCIPAL DISPLAY PANEL - Bottle Label

NDC 61958-0401-1

Viread[®]

(tenofovir disoproxil
fumarate) Tablets, 300 mg
30 tablets
Rx only



PRINCIPAL DISPLAY PANEL - Bottle Label

NDC 61958-0401-1

Viread[®]

(tenofovir disoproxil
fumarate) Tablets, 300 mg
30 tablets
Rx only

